EP 0,037,318 A1

Translated from French by the Ralph McElroy Company, Custom Division
P.O. Box 4828, Austin, TX 78765 USA

Code: 282-38194

EUROPEAN PATENT OFFICE

EUROPEAN PATENT APPLICATION

PUBLICATION NO. EP 0,037,318 A1

Int. Cl.³:	A 61 K 7/06 A 61 K 7/48
Application No.:	81400445.3
Filing Date:	March 20, 1981
Priority:	
Date:	March 21, 1980
Country:	France
No.:	8006369
Date of Publication of the Application:	October 7, 1981 Bulletin 81/40
Designated Contracting States:	Austria, Belgium, Switzerland, Germany, France, United Kingdom, Italy, Liechtenstein, Luxembourg, The Netherlands, Sweden

Applicant: Pierre Fabre S.A.
125, rue de la Faisanderie
F-75116 Paris (France)

Inventors: Henri Cousse
La Foun de los Nobios
Chemin des Lastinos, F-81100 Castres (France)

Gilbert Mouzin
21, rue Sainte-Foy
F-81100 Castres (France)

André Cassan
108, rue des Fontaines
F-31300 Toulouse (France)

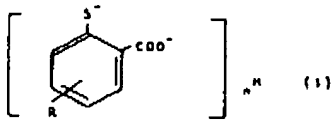
Jean-Paul Ribet
147, rue Goya
F-81100 Castres (France)

Agent:

Jacques Corre et al.
Cabinet Regimbeau
26, Avenue Kléber
F-75116 Paris (France)

NOVEL COMPOSITIONS USEFUL, IN PARTICULAR, IN THE TREATMENT AND PREVENTION OF DANDRUFF AND CONTAINING METAL DERIVATIVES OF THIOBENZOIC ACID

The present invention concerns a composition for external use for the treatment and prevention of skin disorders, especially the treatment and prevention of dandruff of the scalp, characterized in that it contains as the active agent at least one metal derivative of formula:

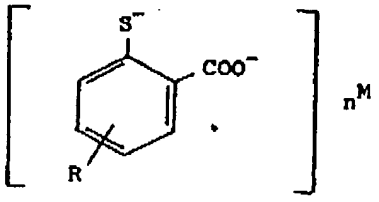


(I)

in which R is hydrogen, a halogen, an alkyl radical or an alkoxy radical; M is a metal cation, and n is a whole or fractional number whose value is such that the derivative of formula I is electrically neutral.

The present invention, realized at the Research Center of Pierre Fabre, concerns novel compositions that are intended for the treatment and prevention of skin disorders and, in particular, for the treatment and prevention of dandruff.

The present invention concerns, in particular, a composition for external use for the treatment and prevention of skin disorders, especially the treatment and prevention of dandruff of the scalp, characterized by the feature that it contains, as the active agent, at least one metal derivative of formula:



I

in which

R is hydrogen, a halogen, an alkyl radical or an alkoxy radical;
M is a metal cation;

n is a whole or fractional number whose value is such that the derivative of formula I is electrically neutral.

Among the halogens that can be present as a substituent, one should cite fluorine, chorine, bromine and iodine, but chlorine is preferred.

The term "alkyl radical" should be understood to mean, in particular, the lower C_1 to C_3 alkyl radicals and, especially, the methyl radical.

The term "alkoxy radical" should also preferably be understood to mean the lower C_1 to C_3 alkoxy radicals and, especially, the methoxy radical.

M is a metal cation of a compatible metal, i.e., [one that is] nontoxic while having good tolerance with respect to the skin; among these cations, one should cite monovalent cations of transition metals such as Ag^+, in which case n = 2, and divalent cations of transition metals such as Zn^{++}, Cu^{++}, Mn^{++}, Fe^{++}, Ni^{++} and Mg^{++} [sic], in which case n = 1.

Thus among the metal derivatives of formula I, one should cite, more particularly, the following derivatives:

- zinc thiosalicylate;
- manganese thiosalicylate;
- nickel thiosalicylate;
- iron thiosalicylate;
- silver thiosalicylate;
- copper thiosalicylate;
- zinc o-thiocresotate;

- zinc 4-methoxythiosalicylate;
- zinc 5-chlorothiosalicylate.

The derivatives of formula I can be prepared by known processes, particularly by the action of a salt of the metal corresponding to M on thiosalicylic acid or the corresponding derivative of this acid as the soluble sodium salt, for example; the derivative of formula I crystallizes from the solution.

The compositions for external use in accordance with the present invention are, more particularly, cosmetic compositions, especially antidandruff compositions, antiseborrheic compositions and compositions for the prevention of cutaneous aging. However, the compositions in accordance with the present invention are also usable for the treatment and prevention of skin disorders such as acne, for example.

These compositions can be present in any form whatsoever that is usable externally, for example, a cream, an ointment, a gel, a lotion or a spray in accordance with the type of application that is envisaged. If the objective that is sought is antidandruff activity, then the composition will preferably be a shampoo or a hair lotion.

The various excipients that can be included in the compositions in accordance with the present invention are selected from the known excipients, especially from the cosmetic area, and examples of these will be given below.

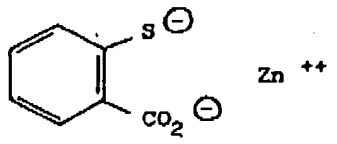
The present invention also concerns the use of the compounds of formula I for the treatment and prevention of skin disorders and, in particular, as an antidandruff agent.

The following examples are intended to illustrate the preparation of certain compounds in accordance with the present invention.

Example 1: Preparation of zinc thiosalicylate

Using good agitation, one adds a solution of 71.88 g (0.25 mol) zinc sulfate heptahydrate in 250 cm^3 of water to a solution of 38.54 g (0.25 mol) thiosalicylic acid in 500 cm^3 [1] N soda (0.5 mol).

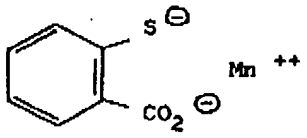
The reaction mixture crystallizes; one stirs for 15 min, filters and washes with water until the sulfate ions have been eliminated. One dries [the material] in an oven at 100°C and recovers 48 g beige crystals (yield 90%) of a product of formula



Molecular formula: $C_7H_4O_2SZn$
Molecular mass: 217.54
Crystals: beige
Melting point: >300°C.

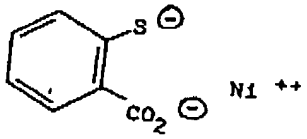
Example 2: Preparation of manganese thiosalicylate

In a similar manner to that described in Example 1, but using manganese chloride tetrahydrate, one obtains the product of formula:



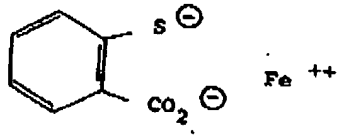
Example 3: Preparation of nickel thiosalicylate

In a similar manner to that described in Example 1, but using nickel chloride, one obtains the product of formula:



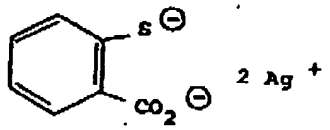
Example 4: Preparation of iron thiosalicylate

In a similar manner to that described in Example 1, but using iron sulfate, one obtains the product of formula:



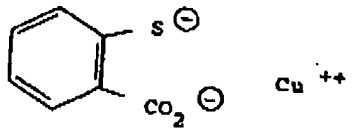
Example 5: Preparation of silver thiosalicylate

In a similar manner to that described in Example 1, but using silver nitrate, one obtains the product of formula:



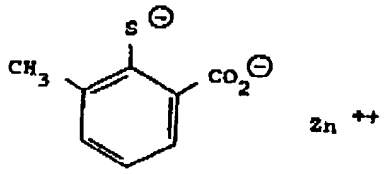
Example 6: Preparation of copper thiosalicylate

In a similar manner to that described in Example 1, but using copper sulfate pentahydrate, one obtains the product of formula:



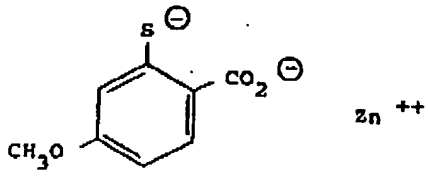
Example 7: Preparation of zinc ortho-thiocresotate

In a similar manner to that described in Example 1, but using o-thiocresotic acid and zinc sulfate, one obtains the product of formula:



Example 8: Preparation of zinc 4-methoxythiosalicylate

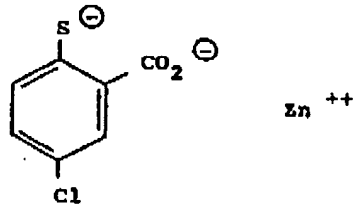
In a similar manner to that described in Example 1, but using 4-methoxythiosalicylic acid and zinc sulfate, one obtains the product of formula:



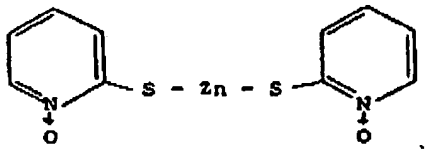
10

Example 9: Preparation of zinc 5-chlorothiosalicylate

In a similar manner to that described in Example 1, but using 5-chlorothiosalicylic acid and zinc sulfate, one obtains the product of formula:



In order to demonstrate the advantageous antidandruff properties of the compounds in accordance with the present invention, one uses as a reference compound the compound currently utilized in antidandruff cosmetic preparations: zinc pyrithione, or zinc omadine, of formula:



$C_{10}H_8N_2O_2S_2Zn$

[molecular] mass: 317

1) Antioxidant capacity

This property is important in the investigation of an antidandruff agent, because it has been shown that one of the causes for the appearance of dandruff arises as a result of oxidation phenomena that can be diminished in the presence of antioxidants.

The measurement of the antioxidant capacity is carried out in accordance with the method described by Carnat and Pourrat (Ann. Pharm. Fr. 1979, 37, No. 3-4, pp. 119-124) by replacing the linseed oil by linoleic acid.

The oxidation of linoleic acid is monitored each day by means of a measurement of the peroxide index, Ip.

a) Peroxide index

One adds 15 mL $CHCl_3$, 20 mL acetic acid of RP grade and then 1 mL saturated aqueous KI solution to a flask containing the linoleic acid. One stirs for 1 min and then allows the flask to stand for 5 min in the dark. After having added 100 mL of water, one titrimetrically analyzes the iodine liberated with 0.01N sodium thiosulfate.

$$Ip = (v - v_0) \times 5$$

v = volume of $Na_2S_2O_3$ added during titration

v_0 = volume of $Na_2S_2O_3$ added during blank trial

Ip is expressed in mmol oxygen/kg fatty acid.

Comment: v_0 has to be close to 0, because a high Ip reveals oxidation of the KI by atmospheric oxygen or by oxygen dissolved in the reagents. In order to avoid this, the reagents and the solvent must be freed of dissolved oxygen by percolating an inert gas through them, this being done in order to obtain comparable results.

The different antioxidants that are to be investigated are suspended in linoleic acid, and the mixtures thus obtained are kept in an oven (60°C).

An Ip [measurement] is carried out every day on the following mixtures:

1 - 1% thiosalicylic acid
2 - 1% Zn pyridinethione
3 - 1% Zn thiosalicylate

The results observed are collected together in Table I below:

Table I. Peroxide index (in mmol D_2 [sic; O_2]/1,000 g linoleic acid)

	0	1 jour (1)	2 jours (1)	3 jours (1)	4 jours (1)
Acide linoléique (essai témoin) (2)	3,2	144	203,7	210,2	209
Acide linoléique + acide thiosalicylique (3)	0,8	117,2	191,9	202,7	204,2
Acide linoléique + pyrithione zinc (4)	0,7	98	174,1	177,6	183,7
Acide linoléique + thiosalicylate de zinc (5)	0,6	45,5	84,4	99,5	103,9

Key: 1 Day(s)
2 Linoleic acid (reference test)
3 Linoleic acid + thiosalicylic acid
4 Linoleic acid + zinc pyrithione
5 Linoleic acid + zinc thiosalicylate

The preceding tests demonstrate the excellent antioxidant activity, relative to zinc pyrithione, of the zinc thiosalicylate in accordance with the present invention.

b) Measurement of the retardation of autooxidation

According to L. Waginaire (Bulletin technique SFPA No. 60), the change in the level of the peroxides takes place in three phases:

1) a slow change in the Ip (not observed with linoleic acid);
2) a rapid change in the Ip (first two days);
3) stabilization and decrease in the Ip.

This latter period appears after several weeks. The author attributes this phenomenon to the formation of carbonyl groups (aldehydes and ketones).

The preceding investigation was modified by using the established protocol of Waginaire, i.e., by dissolving the preservatives in the hot state (60°C) at a level of 1:10,000 in an interesterified [sic] oil that can be dispersed in water (Labrafil - M 1944 CS) and by measuring the Ip each day for 90 days at 60°C. One obtains a curved profile Ip = f(t) comprising a clear autooxidation maximum.

The antioxidant is all the more effective the more the maximum autooxidation is retarded.

The results obtained with the three preservatives that were tested permit one to present the following sequence:

Antioxidant capacity of zinc thiosalicylate > zinc pyrithione > thiosalicylic acid

2) Determination of the partition coefficients at 20°C

(1) Produit	(2) Système	(3) Valeurs de P
(4) Pyrithione zinc	Octanol-eau (5)	0,64
	$CHCl_3$ - eau (6)	0,30
Thiosalicylate (7) zinc	Octanol-eau (5)	0,21
	$CHCl_3$ - eau (6)	0,05

Key: 1 Product
2 System
3 Values of P
4 Zinc pyrithione
5 Octanol-water
6 $CHCl_3$-water
7 Zinc thiosalicylate

3) Maximum solubility in water at 20°C

Determined by spectroscopy in water at 20°C:
Zinc pyrithione = 2 mg % mL
Zinc thiosalicylate = 1.80 mg % mL.

It is interesting to have a product available that is only slightly soluble in water and that is, in general, better tolerated locally.

4) Concentration with respect to zinc

Composés (1)	% zinc
Pyrithione zinc (2)	20,5
Thiosalicylate zinc (3) (exemple 1)	30
Thiocrésotinate zinc (4) (exemple 7)	28,1
(5) Exemple 8	26,3
(5) Exemple 9	25,7

Key: 1 Compounds
2 Zinc pyrithione
3 Zinc thiosalicylate (Example 1)
4 Zinc thiocresotate (Example 7)
5 Example

The compounds in accordance with the invention contain up to 50% more zinc than zinc pyrithione.

Local tolerance

This has been determined, relative to zinc pyrithione, for the compounds of Examples 1, 7, 8 and 9.

The tolerance was investigated on 5 adult albino guinea pigs for each compound. The use of the product 3 times per week for 2 weeks on their unshaved flanks does not provoke any reaction at all.

For 4 products of the invention, the cutaneous tolerance is better than with zinc pyrithione.

Applications

Taking account of their perfect local tolerance, their high antioxidant capacity and the proportion of zinc, these molecules are usable in cosmetology, and more particularly, in the treatment of dandruff, seborrhea and cutaneous aging.

By way of examples which are not limitative, we give below a few formulations in which the compounds in accordance with the present invention can be used alone or in combination with other compounds, that are endowed with cosmetic properties, in appropriate excipients.

Formula 1: Shampoo

- Zinc thiosalicylate, 0.5-3%
- Sodium alkylethoxysulfosuccinate
- Hypoallergic perfume
- Excipients pH 7 ± 0.5.

Formula 2: Dry shampoo

- Zinc 4-methoxythiosalicylate, 2 ± 1.5%
- Excipient and anionic surfactant

Formula 3: Cream for the treatment of cutaneous aging

- Zinc thiosalicylate 1%
- Vitamin A glycerine ester
- Glycerine
- Prodermium (moisturizing agent)
- Natural perfume based on plant essential oil
- Emulsifying excipient

Formula 4: Hair lotion

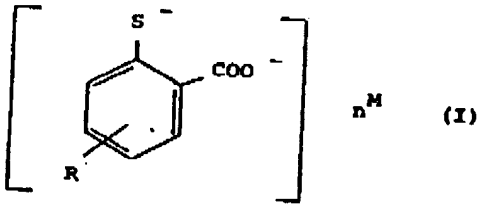
- Zinc thiosalicylate
- Excipient

Formula 5: Antiacne composition

- Mg 5-chlorothiosalicylate, 2-5%
- Corn oil
- Sweet almond oil

Claims

1. Composition for external use for the treatment and prevention of skin disorders, especially the treatment and prevention of dandruff of the scalp, characterized in that it contains as the active agent at least one metal derivative of formula:



(I)

in which

R is hydrogen, a halogen, an alkyl radical or an alkoxy radical;

M is a metal cation;

n is a whole or fractional number whose value is such that the derivative of formula I is electrically neutral.

2. Composition in accordance with Claim 1, characterized in that R is hydrogen, chlorine, a methyl radical or a methoxy radical.

3. Composition in accordance with one of the Claims 1 and 2, characterized in that M is a monovalent or divalent cation of a transition metal and n is equal, respectively, to 2 or 1.

4. Composition in accordance with Claim 3, characterized in that M is selected from Zn^{++}, Cu^{++}, Mg^{++}, Mn^{++}, Fe^{++}, Ni^{++} and Ag^{+}.

5. Composition in accordance with Claim 4, characterized in that the metal derivative of Formula I is selected from:

- zinc thiosalicylate;
- manganese thiosalicylate;
- nickel thiosalicylate;
- iron thiosalicylate;
- silver thiosalicylate;
- copper thiosalicylate;
- zinc ortho-thiocresotate;
- zinc 4-methoxythiosalicylate;
- zinc 5-chlorothiosalicylate.

6. Composition in accordance with one of the Claims 1 to 5, characterized in that it is intended for the treatment of the scalp.

7. Composition in accordance with Claim 6, characterized in that it is present in the form of a shampoo or hair lotion.

European Patent Office

Application Number

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl.⁵)
	Experientia, Vol. 22, No. 5, May 15, 1966 Basel, Switzerland A.D. Inglot et al.: "Effect of choline salicylates and some other analogs of salicylic acid on the replication of EMC virus in vitro." pp. 322-324 * Page 322, right-hand column, page 323, Compound III; page 323, right column, last paragraph - page 324, left column, 1st paragraph *	1	A 61 K 7/06 7/48
A	FR-A 1,594,624 (Luzier Inc.) * Summary *	1	

TECHNICAL FIELDS SEARCHED (Int Cl.⁵)

A 61 K 7/06
7/48
31/19
31/28
31/295
31/30
31/315
C 07 C 149/40

The present search report has been drawn up for all claims.

Place of search	Date of completion of the search	Examiner
The Hague	July 2, 1981	WILLEKENS

CATEGORY OF CITED DOCUMENTS

X: Particularly relevant if taken alone.
Y: Particularly relevant if combined with another document of the same category.
A: Technological background.
O: Non-written disclosure.
P: Intermediate document

T: Theory or principle underlying the invention.
E: Earlier patent document, but published on, or after the filing date.
D: Document cited in the application.
L: Document cited for other reasons.

&: Member of the same patent family, corresponding document